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Gene Section
Mini Review

AXIN2 (axin 2)

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Identity

Hugo: AXIN2
Other names: axil (mostly in rat); conductin; DKFZp781B0869 (single database entry only); MGC126582 (single database entry only)
Location: 17q24.1

DNA/RNA

Description

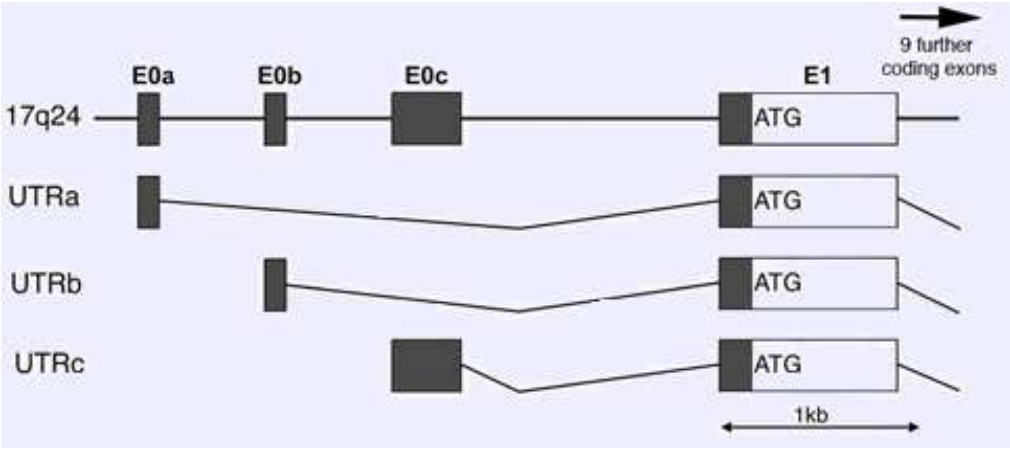
The AXIN2 gene spans about 35 kbp including 10 coding exons and 3 non-coding 5' exons (E0a, 0b and 0c; see above). Nearby genes: about 70 kbp upstream is CCDC46 (coiled-coil domain containing 46), about 300 kbp downstream is RGS9 (regulator of G-protein signalling 9). In addition, there is a putative gene that overlaps the AXIN2 non-coding 5' exons and coding exon 1 (E1) and is transcribed from the same strand (Gnomon model hmm119498); there is no published data on whether this is actually expressed.

Transcription

Transcription occurs from three separate promoters leading to initiation at each of the three non-coding 5' exons. mRNAs are spliced so that each non-coding exon is expressed separately, rather than in combinations. It is unclear whether transcription can initiate at the first coding exon (E1). Promoters can be activated by TCF transcription factors binding at multiple sites and by E2F1 binding at up to 4 sites, although E2F1 can also induce transcription in the absence of consensus sites. It has been reported that exon 6 can be omitted in an alternatively-spliced form.

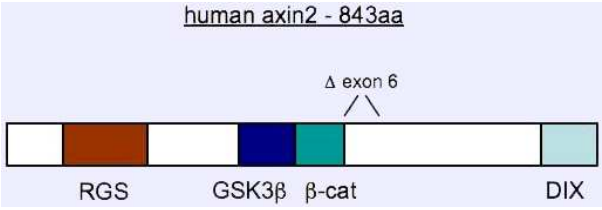
Pseudogene

None identified.



The 5' end of the human AXIN2 gene. An alignment of human genomic DNA (top line) with the 5' end of different Axin2 mRNA variants. Exons are shown as boxes (non-coding: filled; coding: open) and the translational start codon is marked (ATG).

Protein



Description

Human Axin2 is an 843 amino acids protein (777 amino acids from delta exon 6 mRNAs) containing an RGS domain (regulator of G protein signalling; amino acids 81-200), a GSK-3 beta binding domain (amino acids 327-413), a beta-catenin binding domain (amino acids 413-476), and a DIX domain (domain in dishevelled and axin; amino acids 761-843).

Expression

Expression appears to be ubiquitous in adult tissues (although at differing levels), but is limited to specific regions during embryonic development. Expression is regulated at multiple levels including transcription, mRNA stability, translation and protein stability.

Localisation

Axin2 protein has been localised to the cytoplasm, the nucleus and the mitotic spindle.

Function

Molecular functions:

1) Axin2 acts as a negative regulator of canonical Wnt/TCF signalling by enhancing formation of the beta-catenin destruction complex. Since expression of Axin2 is itself activated by canonical Wnt/TCF signalling, this results in a negative feedback-loop that restricts TCF activity.

2) Axin2 may influence TCF activity by re-localising beta-catenin to the cytoplasm.

3) Activity of the GSK-3 beta target snail1 can be regulated by Axin2's ability to influence the nucleo-cytoplasmic localisation of GSK-3 beta.

4) Axin2 binds polo-like kinase 1 (PLK1) during mitosis and influences the accuracy of chromosome segregation.

Cellular/physiological functions:

1) Axin2 expression oscillates during early embryogenesis in response to Wnt3a this is required to achieve correct the temporal TCF activity to allow somatogenesis.

2) A requirement for Axin2 for correct calvarial morphogenesis and craniosynostosis has been revealed in Axin2 -/- mice.

3) Axin2 appears to act as a tumour suppressor, and somatic mutations have been seen in many different tumour types (see below).

Homology

Axin2 is 44% identical to axin in mice and knock-in experiments suggest that the proteins can be functionally equivalent.

Mutations

Note: A large number of different mutations in the AXIN2 gene have been identified. In many cases (but not all) these lead to premature translational termination and protein truncation. Truncated Axin2 protein is more stable than the wild type, while there has been speculation that the mRNA may be less stable.

Germinal

Heterozygous germ line mutations in exon 7 that lead to premature termination are associated with familial tooth agenesis and a predisposition to colorectal cancer. Further germ line polymorphisms associated with familial tooth agenesis have been identified in exons 2 and 7. A polymorphism within exon 1 has been identified that is associated with risk of lung cancer. Many other polymorphisms that have yet to be associated with any function have been detected.

Somatic

The genomic region containing the AXIN2 gene shows loss of heterozygosity and re-arrangements in a variety of cancers. In addition somatic point mutations and deletions have been identified in colorectal cancer, hepatocellular carcinomas, ovarian endometrioid adenocarcinomas and hepatoblastomas. Many of these mutations/deletions result in translation of truncated proteins that are likely to be functionally inactive, although one report has suggested that these truncated proteins have a dominant negative activity.

Implicated in

Colorectal cancer (CRC)

Oncogenesis

Axin2 is often over-expressed in CRC as a result of the deregulation of canonical Wnt/beta-catenin signalling that is an early event in CRC development (usually caused by mutations/deletions in APC or beta-catenin). Somatic inactivating mutations within Axin2 have been reported in CRC and theoretically these could contribute to further deregulation of Wnt/beta-catenin suggesting that Axin2 is a tumour suppressor. However mutations have only been seen in microsatellite unstable tumours and often within regions of mono-nucleotide repeats (exon 7), hence whether Axin2 mutations are cause or effect in these tumours remains undetermined. In support of Axin2's role as a tumour suppressor are observations that Axin2 is silenced by promoter methylation in many microsatellite unstable tumours.

As discussed above, heterozygotes for some germ line mutations in AXIN2 are predisposed to CRC although this seems to be involved with only a very small proportion of familial colorectal cancer.

Other cancers (hepatocellular carcinomas, hepatoblastomas, ovarian endometrioid adenocarcinomas)

Oncogenesis

Somatic mutations in Axin2 have been detected in a range of cancer types. It is usually assumed that these lead to partial inactivation of Axin2 function thereby deregulation of canonical Wnt/beta-catenin signalling. In most cases this has not formally been demonstrated, and the contribution of Axin2 mutations to any putative change in Wnt/beta-catenin activity and to the development of these cancers remains mostly unclear.

Familial Tooth Agenesis (see above)

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